REMARKS

At the outset, Applicants wish to thank Examiner Li for taking the time to meet with Applicants' representative, Ms. Chalin A. Smith. The following remarks are in response to the Final Office Action of November 20, 2003 and the personal interview of May 10, 2004. In particular, Applicants have amended claims 1, 11, 12, 13, 16, 20, 28, 29, 33, 41, and 42 to recite an immunodeficiency viral protein (as opposed to a Sendai viral protein), that acts as the antigen and induces the antigen specific cellular immune response. Support for this amendment is found in the specification as originally filed, for example, as found at p. 9, lines 15-36. Applicants submit that no new matter has been added by the current claim amendments.

Upon entry of this amendment, claims 1-5, 7, 9, 11-20, 24, 26, 28-33, 37, 39, and 41-61 are pending in the application, as claims 46-61 were withdrawn from consideration subject to an election of species.

Election of Species

In the previous Office Action, the Examiner indicated that claims 46-61 were drawn to a species of invention that was independent and distinct from the invention as originally claimed. Accordingly, under the doctrine of election by original presentation, claims 46-61 were withdrawn from consideration as being directed to a non-elected invention.

Applicants respectfully submit that that the patentably distinct species set forth in the pending claims are sufficiently related such that no serious burden would be imposed upon the Examiner to search the entire claim set and, accordingly, request reconsideration of the election of species. In any event, Applicants respectfully submit that independent claims 1, 2, 5, 11, 16, 17, 20 and 33, from which non-elected claims 46-61 directly or indirectly depend, constitute allowable generic claims that link the species embraced thereby. As noted in 37 CFR § 1.141 and MPEP § 809.02(a), upon the allowance of a generic claim, Applicants are entitled to consideration of claims to a reasonable number of additional species which are written in dependent form or otherwise include all the limitations of an allowed generic claim. Accordingly, Applicants request that the non-elected claims be considered upon indication of an allowable generic claim.

Rejections under 35 U.S.C. § 103

At the outset, Applicants believe that the above claim amendments render the pending art rejections moot. Specifically, the claims, as presently amended, require a recombinant Sendai virus vaccine vector encoding an immunodeficiency viral protein (as opposed to a Sendai viral protein) as vaccine antigen. As discussed in the personal interview, the prior art fails to provide a reasonable expectation of success for vaccine efficacy using such a vector, since Hurwitz discloses only live, wild-type Sendai virus as a vaccine antigen and makes no suggestion that recombinant Sendai virus would be

suitable as a vaccine vector for delivery of exogenous vaccine antigens such as immunodeficiency viral proteins.

In the event that the Examiner requires further explanation, Applicants submit the following comments:

Flanagan in view of Seth, Hurwitz and Yu:

The Examiner rejected claims 1-5, 7, 9, 16-20, 24, 26, 28-33, 37, 39, and 41-45 under 35 U.S.C. § 103(a) as being obvious over Flanagan et al. (JGV, 1997) in view of Seth et al. (PNAS, 1998), Hurwitz et al. (Vaccine, 1997) and Yu et al. (Genes Cells, 1997).

The Examiner relies on Flanagan for teaching the use of an adenovirus expressing SIV gag to achieve a long lasting immune response in mice. The Examiner admits that Flanagan neither teaches the use of a recombinant Sendai virus vector nor the use of a gag-pol fusion protein as claimed. On this basis alone the rejection should be withdrawn. To cure these deficiencies, the Examiner next relies on Seth, Hurwitz, and Yu. Specifically, the Examiner relies on Seth for teaching a vaccinia virus vector expressing gag-pol fusion polypeptides, Hurwitz for teaching immune response advantages of the Sendai virus, and Yu for teaching a Sendai viral vector deficient in the V gene.

M.P.E.P § 2141 (citations omitted) states:

> When applying 35 U.S.C. § 103, the following tenets of patent law must be adhered to:
>
> A. The claimed invention must be considered as a whole;
> B. The references must be considered as a whole and must suggest the desirability and thus the obviousness of making the suggested combination;
> C. The references must be viewed without the benefit of impermissible hindsight vision afforded by the claimed invention; and
> D. The combination must have a reasonable expectation of success.

Applicants respectfully submit that the instant obviousness rejection does not adhere to these requirements.

First, regarding tenet (A), it appears that the Examiner has not considered the invention as a whole. Instead, the Examiner appears to view the invention as a collection of discrete elements, each of which is purportedly found in the prior art. The Examiner instead has selected bits and pieces of four separate references and summarily concluded that one skilled in the art could combine them, in a precisely described manner, to arrive at the claimed invention. In determining the differences between the prior art and the claims, the question is not whether the differences themselves would have been obvious but whether the claimed invention as a whole would have been obvious. See M.P.E.P. § 2141.02 as well as *Stratoflex, Inc. v. Aeroquip Corp*, 713 F.2d 1530, 218 USPQ 871 (Fed. Cir. 1983) and *Schenck v. Nortron Corp.*, 713 F.2d 782, 218 USPQ 698 (Fed. Cir.

1983). The mere fact that select aspects of the claimed invention separately exist in the art does not necessarily lead to a conclusion of obviousness.

In this case, the Examiner parses the claim into its individual elements (e.g., delivery vector, vaccine antigen, administration route). In addition, the Examiner ignores the fact that the specific combination described and claimed has distinct advantages that make it superior to other immunodeficiency virus vaccines. For example, the recombinant Sendai virus vaccine vector as claimed: (a) is able to remarkably decrease viral loads in chronic phase (see, for example, the Specification, at p. 3, lines 25 – 28) and yields remarkable infection protection using only a single antigen (see, for example, the Specification, at p. 4, lines 34 – 36); (b) is less cytotoxic and yields antigen expression levels that are higher in mammalian cells (see, for example, the Specification, at p. 3, lines 35 – 36); (c) is able to induce antigen specific cellular immune responses and induce systemic mucosal immunity *in vivo* using lower dosages (see, for example, the Specification, at p. 4, lines 27 – 29 and p. 5, lines 21 – 23); and (d) is non-pathogenic to humans and relatively safe, having a localized and well-controlled antigen expression pattern (see, for example, the Specification, at p. 5, lines 15 – 20 and p. 8, lines 5 – 7). In other words, the Sendai virus is unexpectedly superior to prior art vaccine vectors, such as adenovirus and vaccinia virus, in that, due to its high transgene expression level and high infectivity of the nasal cavity (i.e., mucosal tissues), a small dose can produce substantial, protective, and antigen-specific vaccine response. Accordingly, it appears that the instant

rejection is a result of piecemeal analysis and not the result of consideration of the invention as a whole. For this reason, the suggestion of obviousness is improper.

Second, regarding tenet (B), it appears that the Examiner has not considered the references as a whole, including portions that teach away from the suggested combination. Explicit factual findings on motivation or suggestion to select the claimed invention must be articulated in order to support an obviousness grounds of rejection. See *In re Dillon*, 919 F.2d 688 at 693, 16 USPQ2d 1897 at 1901 (Fed. Cir. 1990). Conclusory statements of "similarity" or "motivation", without specifically articulated rationale and evidentiary support, do not constitute sufficient factual findings. In other words, to support a conclusion that a claimed invention is obvious, either the references must expressly or impliedly suggest the claimed invention or the Examiner must present a convincing line of reasoning as to why one skilled in the art would have found the claimed invention to be obvious in light of the teachings of the references.

In this case, the Examiner has identified four separate references and then summarily concluded that the Examiner would be motivated to combine them, in a precisely described manner, all to arrive at the claimed invention. The instant obviousness rejection does not include specific reasons explaining why one would have been motivated to combine this plurality of discrete, often divergent, teachings as suggested. Furthermore, it appears that the Examiner has overlooked those aspects of the references that are in conflict with each other or the claimed invention. Accordingly,

Applicants respectfully submit that not only is there no motivation to combine the four references as suggested, but even if the references were combined as suggested, one would not arrive at the invention of the pending claims.

For example, the Examiner states that it would have been obvious to substitute and/or combine the recombinant adenoviral vector of Flanagan or vaccinia vector of Seth with a recombinant Sendai viral vector and deliver such via intranasal inoculation with a reasonable expectation of success "given the numerous carrier vectors known in the art ... all proven to be effective for mucosal vaccination for viral infection" (see the Final Rejection, at p. 5, lines 1-8). However, it appears that the Examiner has not considered the cited references as a whole because none of the cited prior art supports this conclusion. Specifically, neither Hurwitz nor Yu, the only two cited references related to Sendai virus, describe it as a suitable carrier (i.e., delivery) vector for vaccine antigens, much less as a suitable vector for mucosal vaccination against an immunodeficiency virus capable of eliciting an antigen-specific cellular immune response as claimed. In fact, contrary to the Examiner's suggestion, at the time of invention, Sendai virus was not known as carrier vector for exogenous vaccine antigens, nor was it known to be an effective means for mucosal vaccination against infection with a foreign virus.

Importantly, Hurwitz does not even describe Sendai virus as a vector. Rather, Hurwitz describes live, wild-type Sendai virus *per se*. Because of its close relation to hPIV in terms of sequence and structure, Hurwitz considers the Sendai virus *per se* to be

a candidate for a human vaccine against hPIV-1. Accordingly, in this context, the Sendai virus acts as a vaccine antigen and not as a vaccine vector. Specifically, the goal of Hurwitz is the induction of immune response against Sendai viral antigens to promote immunity against hPIV-1. This is in stark contrast to viral vectors, such as those disclosed by Flanagan and Seth, wherein induction of immune response against the proteins of the viral vector itself is considered to be an unfavorable event. Thus, when one considers the Hurwitz reference as a whole, there is clearly no suggestion of using the Sendai virus even as an expression vector for *in vitro* purposes, much less as a carrier vector for delivering and expressing exogenous viral antigens, particularly *in vivo*.

The Examiner has similarly misinterpreted the teachings of the Yu reference. Contrary to the Examiner's suggestion, Yu does not describe Sendai virus as a "carrier" or "delivery" vector. Rather, Yu describes a Sendai virus based expression system for efficiently producing large quantities of high quality protein *in vitro*. Importantly, there is no discussion of using the Sendai virus as a carrier vector for delivering a vaccine antigen and inducing an antigen-specific cellular immune response thereto. In fact, there is absolutely no discussion of any immune related applications of the vector, much less *in vivo* applications as claimed. Thus, when one considers the Yu reference as a whole, there is clearly no suggestion of using the Sendai virus as a carrier vector for delivering exogenous viral antigens to host cells so as to induce a cellular immune response specific thereto as required by the pending claims.

On the issue of motivation, according to M.P.E.P. § 2143.01, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available in the art, to modify a reference or to combine reference teachings. The mere fact that references can be combined or modified does not render the resultant combination obvious unless the prior art also suggests the desirability of the combination. *In re Mills*, 916 F.2d 680, 16 USPQ2d 1430 (Fed. Cir. 1990). In this case, the Examiner relies on various advantages suggested by each reference and then summarily concludes that one skilled in the art would have been motivated to combine the references as suggested (see, for example, the Final Rejection at p. 4, second paragraph). However, the Examiner fails to present the requisite "convincing line of reasoning" explaining why one skilled in the art would have selectively combined these often conflicting references in the specific manner suggested. In fact, in certain instances, there is no suggestion that these divergent teachings of the prior art should or even could be combined as suggested.

For example, on combining the Hurwitz and Yu teachings, the Examiner states that Hurwitz teaches the advantage of using Sendai virus as a potential human vaccine because of its long lasting effect stimulating B-cells as well as CTL response and relies on the discussion at the bottom of p. 539 for support. As discussed above, Hurwitz does not describe Sendai virus as a vaccine vector; rather, Hurwitz describes Sendai virus as a vaccine antigen. Nevertheless, when reading the noted passage in context, it is clear that this is an advantage associated with live virus immunizations (as opposed to inactivated

virus) and not an advantage associated with Sendai virus *per se*. Conversely, the Sendai virus described by Yu et al. is a mutant Sendai viral expression vector in which the V gene has been knocked out (i.e., V(-)SeV), a strain of virus Applicants' describe as greatly attenuated (i.e., weakened or inactivated) in mice (see, for example, the Specification at p. 4, lines 35-36). Accordingly, one skilled would not have been motivated to combine the Hurwitz and Yu teachings as the Examiner suggests because the resulting combination would not retain the beneficial properties described by Hurwitz, namely the ability to provide a long lasting effect B-cell as well as CTL response.

Furthermore, the Examiner indicates that Yu suggests the use of the vector in "immunological studies"; see the Final Rejection, p. 6. However, in the context of the Yu reference, the "immunological studies" referred to comprise immunological studies of the purified glycoprotein, gp120, and not the vector *per se*. There is simply no suggestion anywhere in the Yu reference that the recombinant Sendai virus vector would be suitable for mucosal vaccination against immunodeficiency virus, capable of inducing an antigen specific cellular immune response.

On the issue of combining the Flanagan, Seth, and Yu references, none of the references suggest the desirability of the claimed invention nor that the modifications would result in a successful therapy. Specifically, contrary to the Examiner's suggestion, the Flanagan, Seth, and Yu vectors are not analogous equivalents that may be routinely substituted for each other. As discussed above, they are not all "carrier vectors" of

vaccine antigens proven to be effective for *in vivo* mucosal vaccination against viral infection or capable of eliciting antigen-specific cellular immune responses, either *in vitro* or *in vivo*. Moreover, whereas Flanagan's adenovirus and Seth's vaccinia virus are both double stranded, linear DNA viruses, the Sendai virus described by Yu is a non-segmented, negative strand RNA virus. RNA and DNA viruses differ not only in terms of structure but also in terms of functionality and biosynthesis. For example, whereas a host's cellular enzymes transcribe adenoviral DNA in the host's nucleus, Sendai viral RNA is copied in the cytoplasm by viral enzymes to make mRNA. This distinction is particularly critical. Since replication occurs in the cytoplasm without a nuclear phase, the Sendai viral vector can efficiently express even lentiviral structural proteins such as Gag, Pol, and Env in Rev-independent manner. More importantly, unlike the DNA viral vectors of the references of record, Sendai viral vectors infect non-dividing cells and express foreign genes vigorously (see, for example, the Specification at p. 4, lines 18-23).

Furthermore, adenovirus and vaccinia virus often need to be modified to be replication compromised or replication incompetent for safety purposes. Conversely, because Sendai virus requires an envelope-processing protease for its replication, its replication tropism is restricted to particular tissues, such as epithelia of the airway. Since no spread into other tissues is expected, the Sendai viral vector is considered to be safe even in a replication competent form (see, for example, the Specification, at p. 5, lines 15-20). Accordingly, in light of the differences in terms of structure and function, one

skilled in the art would not have considered the viruses disclosed by Flanagan, Seth and Yu to be equivalents and would not have been motivated to exchange one for the other.

In sum, Applicants respectfully submit that not only is there no motivation to combine the references as suggested, but even if the references were combined as suggested, one would not arrive at the invention of the pending claims. For these reasons, the suggestion of obviousness is improper.

From the above discussion, it appears that the Examiner has disregarded tenet (C). Since clear indications of motivation are missing, the motivation to combine can only arise from Applicant's own disclosure and not from the prior art references themselves. In other words, the Examiner's conclusion of obviousness in this case is based on improper hindsight reasoning, constituting improper hindsight analysis that utilizes knowledge gleaned from Applicant's disclosure and not from the references of record. For this reason, the suggestion of obviousness is improper.

Finally, regarding tenet (D), there is no reason to believe that the combination would be successful, particularly in light of the conflicting teachings. As discussed above, none of the cited prior art references suggest that the Sendai virus would be suitable as a vaccine vector, for delivering and expressing exogenous vaccine antigens and inducing a cellular immune response specific thereto, either *in vitro* or *in vivo*. Both Flanagan and Seth emphasize the importance of stimulating viral antigen-specific cytotoxic T lymphocytes (CTLs), both for containing the spread of virus and maintaining freedom

from disease. However, neither Hurwitz nor Yu (nor Kast cited below) disclose or suggest that Sendai virus would be suitable as a vaccine vector, capable of inducing a protective, antigen-specific, cellular immune response. In fact, the Kast reference casts doubt on the ability of wild-type Sendai virus to ubiquitously induce a specific CTL response to Sendai viral proteins, noting that the bm14 mouse demonstrated a virus specific CTL response while the bm1 mouse did not (see Kast, at p. 3186, col. 2). Likewise, the Yu disclosure casts doubt on the ability of the Sendai virus to express foreign proteins other than gp120, noting the recorded failure of a Sendai virus vector to yield functional luciferase (see Yu, at p. 463, col. 2). Taken together, these references indicate that the properties and activities of the Sendai virus are difficult to predict *a priori.*

Furthermore, the advantages discussed by Hurwitz and cited by the Examiner (i.e., long lasting reservoir of memory B-cells, long lived CTL responses) are attributable to live virus (as opposed to inactivated and attenuated virus) immunizations, and are not to the Sendai virus *per se.* Conversely, the Sendai virus described by Yu et al. is an attenuated (i.e., weakened or inactivated) strain (see, for example, the Specification at p. 4, lines 35-36).

Accordingly, one skilled would not have expected the resulting combination of Hurwitz and Yu to retain the beneficial properties described by Hurwitz. Moreover, since the findings of Hurwitz relate to the use of live, wild-type, Sendai virus as a vaccine

antigen and not as a vaccine vector for the delivery of exogenous antigens, at the time of invention, one skilled in the art could not have reasonably predicted that a recombinant Sendai virus vector could induce a cellular immune response specific to an exogenous immunodeficiency viral protein as required by the instant claims. Accordingly, as one skilled in the art could not have predicted with any reasonable degree of certainty that a recombinant Sendai viral vector would be successful at inducing a protective, antigen-specific cellular immune response, and therefore be suitable as an immunodeficiency virus vaccine, the suggestion of obviousness is improper.

In conclusion, Applicants respectfully submit that the obviousness rejection is flawed, lacking both legal and scientific foundation. As discussed above, the instant combination of references is improper. Not only has the Examiner failed to provide a motivation to combine the references as suggested, but the suggested combination would not have a reasonable expectation of success considering the unpredictability and complexity of the art. Thus, Applicants respectfully submit that the instant obviousness rejection should be withdrawn.

Flanagan in view of Seth, Kast and Yu:

The Examiner has also rejected claims 11-13 and 15 under 35 U.S.C. § 103 as being obvious over Flanagan et al. in view of Seth et al., Kast et al., and Yu et al. The Flanagan, Seth, and Yu references are discussed above. The Examiner relies on Kast

for teaching the transfection of dendritic cells with Sendai virus.

Applicants respectfully submit this rejection is similarly flawed for the reasons given above. Specifically, as discussed above, none of the cited references, alone or in combination, suggest the use of Sendai virus as a vaccine vector for delivering a foreign viral antigens and inducing a cellular immune response specific thereto. Also as noted above, Yu describes Sendai virus as an expression vector for efficiently producing large quantities of high quality protein *in vitro*. There is no suggestion of using the Sendai virus as a carrier vector for delivering and expressing vaccine antigens so as to elicit antigen-specific cellular immune responses either *in vitro* or *in vivo*. Kast does not cure this deficiency. Like Hurwitz cited above, the Kast reference describes live, wild-type Sendai virus, wherein the Sendai virus serves as a vaccine antigen and not as a vaccine vector. Importantly, there is no suggestion in Kast of using the Sendai virus as a recombinant viral vector to express foreign vaccine antigens. Accordingly, since Kast teaches away from the claimed invention of a recombinant Sendai viral vector encoding an immunodeficiency viral protein, it cannot cure the deficiencies of the combination of Flanagan, Seth, and Yu discussed above.

Moreover, as noted above, Kast casts doubt on the ability of wild-type Sendai virus to ubiquitously induce an antigen-specific CTL response to Sendai viral proteins, noting that the bm14 mouse demonstrated a virus specific CTL response while the bm1 mouse did not. Accordingly, one skilled in the art could not have predicted with any degree of

certainty that a recombinant Sendai viral vector could successfully induce a protective, antigen-specific cellular immune response, and, therefore, be suitable as an immunodeficiency virus vaccine.

Furthermore, it appears that the Examiner has overlooked select claim limitations. Specifically, while Kast indeed describes infecting a dendritic cell *in vitro* with live, wild-type Sendai virus, none of the four cited reference disclose or suggest Applicants' required step (b) of subsequently "contacting the antigen presenting cell with a T helper cell and cytotoxic T cell, thereby inducing a cellular immune response". Accordingly, since none of the references, alone or in combination, disclose or suggest Applicants' claimed invention, and cannot render the claimed invention *prima facie* obvious.

Finally, on the issue of motivation, the Examiner concludes that "the ordinary skilled artisan would have been motivated to modify the method[s of the prior art] for their particular needs of investigation, i.e., a particular vector of interest or a particular antigen of interest, etc." However, this conclusion ignores the requirement that the references *themselves* suggest the desirability of the combination. As discussed above, the Examiner is not free to pick and choose components from an array of references and combine them at will, absent express motivation or suggestion to do so. Accordingly, the piecemeal analysis of the claims presented herein is improper and appears to be the result of impermissible hindsight reasoning.

In sum, in light the above, Applicants respectfully submit that not only is there no motivation to combine the references as suggested, but even if the references were combined as suggested, one would not arrive at the invention of the pending claims. Accordingly, Applicants respectfully submit that the instant obviousness rejection is improper and should be withdrawn.

Flanagan in view of Seth, Kast, Yu and Bouttillon:

The Examiner has also rejected claim 14 under 35 U.S.C. § 103 as being obvious over Flanagan et al. in view of Seth et al., Kast et al., and Yu et al. as applied to claim 11, further in view of Bouttillon et al.

Applicants addressed this combination in the previous response. The Examiner notes that one may not show non-obviousness by attacking references individually where the rejections are based on combinations of references. Rather, one must look to the combined teachings. However, as discussed above, it is precisely the suggested combination that is fundamentally flawed. As discussed above as well as the prior response, not only is there no motivation to combine the references as suggested, but even if the references were combined as suggested, one would not arrive at the invention of the pending claims.

Specifically, Boutillon fails to cure the above-noted deficiencies of Flanagan, Seth, Yu, and Kast in terms of teaching Sendai virus as a carrier vector for delivering a foreign

vaccine antigen and inducing a cellular immune response specific thereto, either *in vitro* or *in vivo*. Thus, this rejection is in error for the reasons given above regarding the rejection of claims 11-13 and 15. The Examiner's suggestion that these five references may be seamlessly combined to arrive at the claimed invention is simply not supported by the teachings of the references themselves. As discussed above, piecemeal analysis and hindsight reasoning are improper and cannot be used to support a finding of obviousness. Thus, Applicants respectfully submit that not only is there no motivation to combine the references as suggested, but even if the references were combined as suggested, one would not arrive at the invention of the pending claims. Accordingly, Applicants respectfully submit that the instant obviousness rejection is improper and should be withdrawn.

CONCLUSION

Applicants respectfully submit that the claims as amended herein set forth a novel, non-obvious invention. Accordingly, Applicants respectfully submit that claims 1-5, 7, 9, 11-20, 24, 26, 28-33, 37, 39, and 41-61 as amended herein are in condition for allowance and respectfully petition for an early notice of allowance. However, in the event the Examiner feels that further discussion is merited, the Examiner is cordially invited to contact the undersigned.

Applicants timely filed a Notice of Appeal on May 17, 2004. Enclosed are a Petition to extend the period for submitting an Appeal Brief pursuant to the Notice of Appeal for four months, to and including November 17, 2004 and a check in the amount of the required extension fee. If there are any additional charges or any credits, please apply them to Deposit Account No. 03-2095.

Respectfully submitted,

Date: 17 November 2004

James D. DeCamp, Ph.D.
Reg. No. 43,580

JAN M. TITOR, Ph.D.
Reg. No. 52,290

Clark & Elbing LLP
101 Federal Street
Boston, MA 02110
Telephone: 617-428-0200
Facsimile: 617-428-7045